525 Rec'd PCT/PTO 07 SEP 2000

FORM PTO-1390 (REV. 1-98) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
933-160P	09/623364 NEW

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FI99/00167	March 4, 1999	March 4, 1998

TITLE OF INVENTION

NOVEL DERIVATIVES OF CYCLODEXTRINS

APPLICANT(S) FOR DO/EO/US

KHOMUTOV, Alexei R.; YAKOVLEV, Dmitry Y.; KHOMUTOV, Radii M.; KORPELA, Timo

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 99/45032
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.-1449 and International Search Report (PCT/ISA/210)
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    1.) International Prelimnary Examination Report (PCT/IPEA/409)
    2.) Four (4) sheets of Formal Drawings

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U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 09/623364	PCT/FI99/00167	933-160P

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$970.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	13 - 20 =	0	X **$18.00**	$ 0	
Independent Claims	2 - 3 =	0	X **$78.00**	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		Yes	+ **$260.00**	$ 260.00	
			TOTAL OF ABOVE CALCULATIONS =	$ 1360.00	
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0	
			SUBTOTAL =	$ 1360.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0	
			TOTAL NATIONAL FEE =	$ 1360.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0	
			TOTAL FEES ENCLOSED =	$ 1360.00	
			Amount to be: refunded	$	
			charged	$	

a. ☒ A check in the amount of $ **1360.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703)205-8000

SIGNATURE #32,858

MURPHY, GERALD M., JR.
NAME

#28,977 (GMM)
REGISTRATION NUMBER

/cqc September 1, 2000

09/623364
PATENT
933-160P
534 Rec'd PCT/PTO 01 SEP 2000

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: KHOMUTOV, Alexei R. et al.

Int'l. Appl. No.: PCT/FI99/00167

Appl. No.: New Group:

Filed: September 1, 2000 Examiner:

For: NOVEL DERIVATIVES OF CYCLODEXTRINS

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents September 1, 2000
Washington, DC 20231

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/FI99/00167 which has an International filing date of March 4, 1999, which designated the United States of America.--

IN THE CLAIMS:

Please amend the claims as follows:

Claim 4: Line 1, change "any one of claims 1 and 3" to --claim 1--

Claim 5: Line 1, delete ", 3"

Claim 6: Line 1, delete "or 5"

Claim 7: Line 1, delete "-6"

Claim 9: Line 1, change "claims 1-7" to --claim 1--

Claim 10: Line 1, delete "-7"

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application. The claims have also been amended to delete improper multiple dependents and to place the application into better form for examination. Entry of the present amendment and favorable action on the above-identified application are respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #32,868
Gerald M. Murphy, Jr., #28,977

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GMM/cqc
933-160P

(Rev. 04/19/2000)

SMALL ENTITY DECLARATION

APPLICANT OR PATENTEE KHOMUTOV, Alexei, et al. ATTORNEY'S
SERIAL NO. _____ ☐ PATENT NO. _____ DOCKET No. _____
FILED OR ISSUED _____
FOR "Novel derivatives of cyclodextrins"

I(we) hereby declare that I(we) am(are) entitled to the benefit of small entity status with respect to the above-identified application or patent for purposes of paying reduced fees under 35 USC 41(a) & (b) to the U.S. Patent and Trademark Office.

☒ A. INDEPENDENT INVENTOR
I(we) qualify as a(n) independent inventor(s) as defined in 37 CFR 1.9(c).

☐ B. INDIVIDUAL NON-INVENTOR
I would qualify as an independent inventor as defined in 37 CFR 1.9(c) if I had made the invention.

☐ C. SMALL BUSINESS CONCERN
I am ☐ THE OWNER ☐ AN OFFICIAL of the small business concern identified below and am empowered to act on behalf of the concern. The concern qualifies under 37 CFR 1.9(d) and 13 CFR 121.3-18. Rights under contract or law have been conveyed to and remain with the concern and are exclusive unless a checkmark is placed here ☐ and another Declaration on behalf of another entity is filed herewith.

☐ NON-PROFIT ORGANIZATION
I am an official empowered to act on behalf of the non-profit organization identified below. The organization qualifies under 37 CFR 1.9(e), sub-section: ☐ (1) ☐ (2) ☐ (3) ☐ (4). Rights under contract or law have been conveyed to and remain with the organization and are exclusive unless a checkmark is placed here ☐ and another Declaration on behalf of another entity is filed herewith.

I(we) acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I(we) hereby declare that all statements made herein of my(our) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

A. INDEPENDENT INVENTOR(S) B. INDIVIDUAL NON-INVENTOR(S)

Name of Inventor	Signature	Date
KHOMUTOV, Alexei	A Khomutov	18/9/00
YAKOVLEV, Dmitry		09/11/00
KHOMUTOV, Radii	Radii Khomutov	18/9/00
KORPELA, Timo	Timo Korpela	4.09.00

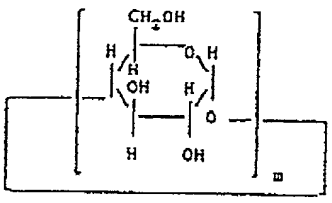
NOVEL DERIVATIVES OF CYCLODEXTRINS

FIELD OF THE INVENTION

This invention relates to the design and synthesis of earlier unknown chemical derivatives of cyclodextrins. The novel compounds exert a number of useful properties which make them applicable as complexants, solubilizers, carbonyl reagents, catalysts, or starting materials for the synthesis of products to be employed in pharmaceuticals, cosmetics, agriculture or in scientific laboratories.

BACKGROUND OF THE INVENTION

α-, β- and γ-Cyclodextrins (α-CD, β-CD and γ-CD) are cyclic oligosacharides consisting of 6, 7 or 8 glucopyranose units, respectively, which are joined together by α(1-4) linkages:



m=6 α-CD
m=7 β-CD
m=8 γ-CD

Cyclodextrins (termed hosts) can imbibe certain molecules or parts thereof (termed guests) into their center cavities. The noncovalent reversible adducts or inclusion complexes formed between the host and the guest can drastically change the properties of the parent guest molecules in diverse ways, such as to increase solubility, decrease volatility, protect from chemical or light-catalyzed reactions, change the location of absorption of complexed drugs in the intestine, etc.

Parent CDs can be covalently modified with a number of reagents to form chemical derivatives. The derivatives can

normally bind similar guest compounds as do the parent CDs, but the properties of the complexes can be changed. A description on the syntheses of CD derivatives and the properties of inclusion complexes of both parent and modified cyclodextrins can be found for instance in *Croft, A.P. & Bartsch, R.A. "Synthesis of Chemically Modified Cyclodextrins", Tetrahedron, 1983, V. 39, No 9, P. 1417-14-71 Szejtli, J. "Cyclodextrin Technology", Kluwer Academic Publishers, Dordrecht,* 1988, pp. 1-450.

Some derivatives of β-CD have a higher solubility than do the parent compound and hence they are often preferable complexants and solubilizers. The potential of the chemical derivatives of β-CD is amplified by its low price as a starting material in comparison to α- and γ-CDs. In contrast to β-CD, the more expensive α- and γ-CDs are readily water soluble and can be used without chemical derivatization for certain purposes. This is illustrated by a number of reports on their complexes with various guest compounds such as steroid hormones, cholesterol or its derivatives and with some drugs. Appropriately alkylated or hydroxyalkylated γ-CDs are also good complexants since their inclusion complexes do not precipitate even at high concentration, as stated in EP 06792.

A large number of papers deals with the syntheses of CD chemical derivatives and their application for divergent purposes (see e.g. *Szejtli, J. "Cyclodextrin Technology" 1988*) clearly showing the importance of the CD derivatives.

SUMMARY OF THE INVENTION

The present invention describes novel CD derivatives carrying specific functions containing an aminooxy (H_2NO-) group covalently connected to a glucopyranose unit of CD. These derivatives have significantly different properties from the CD derivatives known in the prior art and thus

they enlargen the area of application of CDs. The present invention also describes the preparation and use of the said novel CD derivatives as such or complexed with guest molecules or further chemically modified.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to an earlier unknown type of α-, β- or γ-CD chemical derivatives containing the aminooxy (H_2NO-) functional group attached to the CD core and having the general formula 1:

$$CD - (X - Y - ONH_2)_n \qquad \text{formula 1}$$

wherein CD is mono- or polydeoxy α-, β- or γ-CD, carrying in its 6-, 3- and/or 2-position the aminooxy function containing group, and wherein Y is a linker arm connected to deoxy-CD by means of X, which is a direct bond, or a functional group or an atom necessary to connect the linker Y and the deoxy-CD, whereby Y is a direct bond when X is a direct bond. The integer n is equal to or larger than one and cannot be more then 18, 21 and 24 for α-, β- and γ-CD, respectively.

The invention also relates to the compounds of the formula 1, wherein the aminooxy group is in protected form, especially in the form of the 1-ethoxy-ethylideneaminooxy group, $-O-N=C(CH_3)OC_2H_5$, or as the acetone oxime group, $-O-N=C(CH_3)_2$.

The aminooxy-CDs of formula 1 preferably carry one or several H_2NO-groups attached to 6-hydroxy groups (see examples I-IV). By utilizing the different reactivities of primary and secondary hydroxyl groups (primary hydroxyls more reactive than secondary), and if necessary, suitably protected hydroxyl groups, one can discriminate between the reaction at the "top" (primary) hydroxyls and at the

"bottom" (secondary) hydroxyls of the CD molecules (see Croft et. al. supra). These latter types may be important for synthetizing artificial receptors, carriers and catalysts based on the CD-core.

In the compound of the formula 1, CD is a mono- or polydeoxy α-, β- or γ-cyclodextrin. In these compounds, one or more hydroxy groups in the positions 6, 3 and/or 2 of CD are replaced with a (X-Y-ONH_2) fragment, and specifically, together with primary hydroxy groups, one or more secondary hydroxy group can also be substituted with a (X-Y-ONH_2) fragment. The compound according to the invention carrying aminooxy groups can optionally carry further substituents. In the aminooxy-CD, one or more hydroxy groups in the 6-, 3- and/or 2-position may be also substituted e.g. into H_2N-, HS-, -COOH, alkoxy, such as C_1-C_6-alkoxy, aryloxy, aryl being preferably phenyl, benzyl or tolyl, or acyloxy groups, acyl being preferably derived from C_1-C_6-carboxylic or benzoic acid. Alkyl-, aryl- and acyloxy may carry additional functional groups in a side chain or aromatic ring.

Y is a "linker arm, or linking group" and serves as a bridge between the aminooxy (H_2NO-) group and the deoxy-CD moiety. Usually Y is alkylene, alkenylene with one or more double bounds which may be either isolated or conjugated, alkynylene with one or more triple bonds which may be either isolated or conjugated, or arylene or arylalkylene fragments where aryl may be substituted or not substituted, such as phenylene. The alkylene, alkenylene and alkynylene fragments may be linear or branched and preferably contain 2-12 C-atoms in the chain. One or more of the chain members (methylene groups) may be replaced by -NH-, -O-, -S-, -S-S-, -C(O)NH, -C(O)O-, -OP(O)(OH)O-, -S(O)-, SO_2-, -CHR-, where R is preferably alkyl, aryl, -OR', $-NH_2$, -NHR', $-NR'_2$, -OH, -COOH, or $-ONH_2$ groups and where

R′ is alkyl, aryl, or acyl. As R and R′, aryl is preferably phenyl, aryl lower alkyl, such as benzyl or tolyl.

X is preferably -O-, -S-, -NH-, -NR"-, -OCO-, -NH-O-, =NO-, -NHC(O)-, -OP(O)(OH), -R"C=NO-, where R" is alkyl.

R, R′ and R" when having the meaning of alkyl, are preferably linear or branched C_1 - C_6-alkyl, in the meaning of acyl they are preferably derived from linear or branched C_1-C_6-carboxylic acids or benzoic acid.

In the preferred compounds of formula 1, Y is alkylene or alkenylene of 2-12, preferably 2-6 C-atoms, wherein one or more of the chain members may be replaced by -NH-, =N-O-, -O-, -S-, -C(O)NH-, -C(O)O-, or $-CHR_1-$ wherein R_1 is methyl, ethyl or propyl and X is -O-,-S-,-NH-,-OC(O)- or -NH-O-.

The compounds of the formula 1 are week bases (usually the pK of the H_2NO-group is between 4.0 - 6.0) and their solubility is different from the parent CD molecules. As indicated by the pK values, a unique possibility exists to regulate the ionic form of the compounds of formula 1 by solvent acidity near the physiological pH-region. That means that a low pH favours complexation of ionic guest molecules, while high pH-values favour the contribution of non-ionic interactions between host and guest. With related compounds containing alkylamino functions, protonation-deprotonation takes place only at around pH 10 (*Boger,J. et al. Helv.Chim.Acta,1978, V. 61, P. 2190-2218*).

The compounds of formula 1 are carbonyl reagents like other O-substituted hydroxylamines. They react rapidly and quantitatively with various aldehydes and ketones forming oximes which have high stability in water solution at a broad range of pHs. These properties of aminooxy-CDs enable the synthesis of a multitude of CD derivatives in addition to those of the formula 1; for example, immobilization of

CDs on solid supports and subsequent use in the chromatography of various important compounds such as stereoisomers of pharmaceuticals. In addition, oligo- and polymeric materials are readily obtained in a single-step by allowing dialdehydes or diketones to react with di- or polysubstituted aminooxy-CDs in aqueous solution. Such oligo- or polymeric materials are advantageously used as semipermeable or stereoselective membranes, as prolonged-release supports for drugs, sanitary, cosmetics or agricultural materials. Further, the chemical reactivity properties of the aminooxy functions enable one to stabilize CD-complexes of certain physiologically active, highly reactive, aldehydes and ketones - for instance, steroids, prostaglandins and vitamins - by anchoring these into CDs via the oxime bond in addition to the stabilization involved in the host-guest interaction. Since the stabilization effect is cumulative (not additive), the protection conferred by molecular complexation can be drastically increased.

Inclusion complexes in general may be additionally stabilized by means of oxime formation with a suitable aldehyde or ketone. In this case the inclusion complex is first formed which is then reacted with the aldehyde or ketone to form the inclusion complex oxime. Thus the existence of steric hindrance at the cavity entrance may prevent complex from dissociation.

While the oxime bond is stable in water solutions, especially at extreme pH values, it may slowly decompose. This property can be utilized for the slow release of aminooxy-CD bound drugs in the stomach and intestine.

Since aminooxy-CDs are carbonyl reagents, they may inhibit certain crucial enzymes in the metabolism of cells, such as PLP-, pyruvate-, or ketobutyrate-dependent enzymes. The inhibitory potency will depend on the affinity of the coenzyme to protein.

SUBSTITUTE SHEET (RULE 26)

The existence of aminooxy group(s) bound to a CD molecule means that such compounds, like other O-substituted hydroxylamines, are capable of reacting directly with cytidine and adenosine. This was confirmed by the reaction of aminooxy-CDs of formula 1 with 4-thiouracil, 6-mercaptopurine riboside or their derivatives and even cytidines themself (see examples XIII and XIV). Hence, the compounds of formula 1 can be useful for the modification of nucleotides, nucleosides, bases, nucleoside coenzymes and nucleic acids, such as for the formation of nucleotide and nucleoside pyrimidine and purine derivatives of aminooxy CD, wherein the pyrimidine and purine preferably are cytosine or adenine as such, or in the form of their corresponding derivatives.

At neutral and slightly acidic pH, the aminooxy groups of compound of formula 1 are not protonated. The nonprotonated aminooxy groups are strong nucleophiles capable of reacting with an activated carboxyl group (esters, activated esters, mixed anhydrides, anhydrides, etc.) even in water solutions forming stable hydroxamic acids. These can have new useful properties such as the ability to complex certain metal ions. Combined metal ion and CD complexation functions of the aminooxy-CD derivatives may be used for recovering of metal ions from solutions.

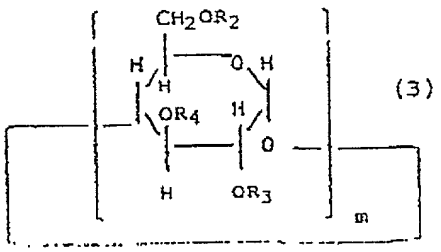
A comparison of the compounds of the present invention with amino group containing CDs *(Boger, J. et al. Helv.Chim.Acta, 1978, V. 61, P. 2190-2218)* demonstrates various advantages for the aminooxy-CDs. The basic disadvantages of the alkylamino-CDs are the high pKs necessitating alkaline reaction conditions during the derivatization reactions and the low stability of the Schiff-base bond between the amino and aldehyde or keto groups in aqueous solutions.

The high nucleophilicity of the aminooxy (H_2NO-) group,

its easy introduction into different sites of the CD molecules with different spacer arms make the aminooxy-CDs and their derivatives promising for the construction of catalytically active CDs.

The compounds of formula 1 can be prepared in different ways, and the present invention is also directed to the processes for the preparation of the novel compounds of the formula 1. Such processes are:

a) alkylation of a corresponding CD derivative with an aminooxy-protected, reactively substituted aminooxy derivative, for example with a compound of the formula 3':



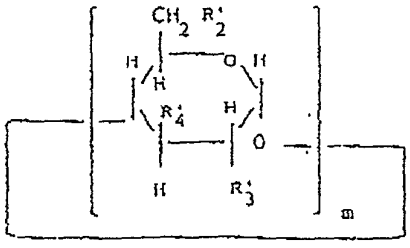
(3)

$$Z - Y - ON=C(CH_3)W \quad (3')$$

wherein R_2, R_3 and R_4 are independently hydrogen, or a substituent (see *Croft et. al. supra*) having no reactive functional group, being typically alkyl, such as C_1-C_6-alkyl, or aryl, such as phenyl, benzyl or tolyl, whereby at least one of the positions 6, 3 and/or 2 contains a hydroxy group, preferably the 6-hydroxy group, W means OC_2H_5 or CH_3, m and Y are as defined above and Z is a reactive group, such as Cl, Br, I, tosyl or mesyl, and optionally removing the protecting group. In this case a compound of the formula 1 is obtained, wherein X is O. In the above formula, when W is OC_2H_5, the compound (3) is protected in the form of the 1-ethoxy-ethylideneaminooxy derivative, and when W is CH_3, in the form of the acetone oxime derivative.

Suitable compounds (3') are e.g. 4-(ethoxyethylideneaminooxy)bromobutene-2, ethyl N-(ω-iodoalkyloxy)acetimidate, the sodium salt of 3-(ethoxyethylideneaminooxy)-2-bromo-bromopropionic acids etc. The compounds (3') are used in alkaline water solutions, using e.g. alkali or alkaline-earth metals, or hydrides, hydroxides, oxides, carbonates, hydrocarbonates thereof; or quaternary ammonium salts, mono-, di- and trialkylamines carrying lower (C_1-C_4) linear or branched alkyl groups being the same or different in alkaline water-organic mixtures (the organic solvent being e.g. a lower (1-4C) alcohol, dioxane, tetrahydrofuran, glyme, cellosolve, dimethylsulfoxide, dimethylformamide) or in liquid ammonia at temperatures from elevated (about 100°C or higher) to ambient temperature. The substitution degree depends on the reaction conditions and the products can have either only few primary hydroxyls being substituted or also secondary hydroxy groups may be involved in the reaction.

b) Alkylating an activated CD-derivative, such as a tosylate, mesylate, halogen derivative, epoxide, activated ester, with an aminooxy-protected, functionally substituted hydroxylamine



$$HX - Y - ON{=}C(CH_3)W \qquad (4')$$

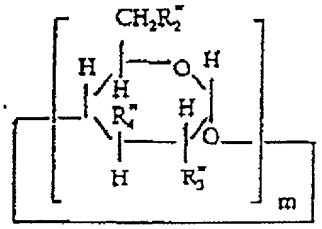
wherein R'_2, R'_3 and R'_4 are hydroxy, or an activated group such as tosyl, mesyl, halogen, ester, epoxide, and X, Y and W are as defined above, and thereafter optionally removing the protecting group. In this reaction, aminooxy CD derivatives are obtained, wherein X is not only O, but also e.g. sulfur or an imino group.

Suitable compounds of the formula (4) are e.g. ethyl N-(ω-mercaptoalkyloxy)-acetimidate, ethyl N-(ω-aminoalkyloxy)acetimidate or ethyl N-hydroxyacetimidate itself.

The activated CD-derivative can also be e.g. a mono- or poly-N-hydroxysuccinimide activated CD-derivative having a -COOH group, which is reacted with the compound of formula 4, where X is a HN-group.

According to an embodiment, one or more of the secondary hydroxy groups in the CD derivative may be unsubstituted or substituted with groups other than activating tosyl, mesyl or halogen, such as with those described above.

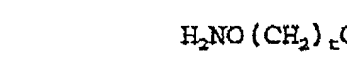
c) Modifying a functionally-substituted CD derivative having of the formula (5)



(5)

wherein at least one of the groups R''_2, R''_3, and R''_4 mean thiol-, amino-, karboxy- etc. group possibly linked directly to deoxy-CD-ring, or mean alkylenoxy- or acyloxy groups, which contain at least one thiol-, amino-, karboxy-, etc. group, or their derivative, and the remaining funtional groups are hydroxyl groups or they have the meaning described in claim 7 for the substituents, and exist, if necessary, in a protected form, typical example being unsubstituted alkoxy, aryloxy, or acyloxy, modified with an appropriate aminooxy protected substituted hydroxylamine according to formula (3'), after which the protecting group(s) are removed, or

d) With modifying such CD-derivative, having one or more keto or aldehyde function at 2-, 3-, and/or 6-position, optionally joined with the above-described linkers, according to bis-aminooxyalkanes of formula (5')



$$H_2NO(CH_2)_tONH_2 \qquad (5')$$

wherein t = 2-12 and wherein one of the methylene groups can be replaced with O or S atoms or -NH- or -S-S- functions.

The cyclodextrin starting materials of the described reactions are well-known from literature.

Selection of a proper protecting group for aminooxy function is crucial, to be succesful in preparing the compounds of formula 1. In the present invention ethyl-N-hydroxyacetimidate fragment or alternatively acetonoxime were employed. Derivatives protected in such a way are stable in a large area of different reaction conditions and the derivatives can be readily converted to corresponding O-substituted hydroxylamines by acid treatment. In the case of ethoxylidene protection the masking group can be removed within 10-60 min at the room temperature with a diluted strong acid, exemplified by hydrohalides, sulfuric phosphoric, nitrous, and paratoluenesulfonic acids. On the contrary, removal of acetonoxime protection demands by refluxing with 20% (w/v) hydrochloric acid.

The invention is described in the following by nonlimiting examples.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1a. Time course of the UV spectra (optical path length 1 mm) of a reaction mixture containing 1 mM 4-thiouracil in 100mM 4-aminooxy-2-butenyl-beta-cyclodextrin (I; see Example I.2) at pH 7.0. Incubation at 20°C is indicated as hours.

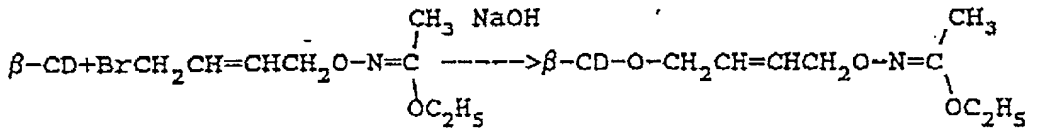
Figure 1b. Time course of the UV spectra (optical path length 1 mm) of a reaction mixture containing 1 mM 4-thiouracil and 100 mM 1-aminooxybutane at 20°C at pH 7.00. Incubation time (hours) is indicated.

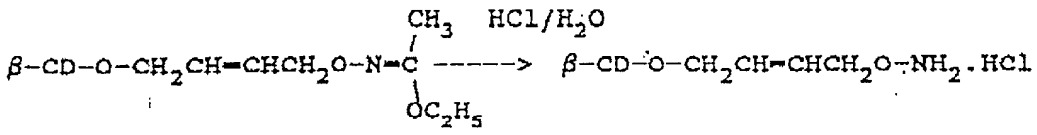
Figure 2a. Time course of the UV spectra (optical path length 1 mm) of a reaction mixture containing 1 mM 6-mercaptopurineriboside with 100 mM 4-aminooxy-2-butenyl-beta-cyclodextrin (see Example I.2). Incubation time (hours) is indicated.

Figure 2b. Time course of the UV spectra (optical path length 1 mm) of a reaction mixture containing 1 mM 6-mercaptopurineriboside with 100 mM 1-aminooxybutane at pH 7.00. Incubation time (hours) is indicated.

Example I

I. 4-Aminooxy-2-butenyl-β-cyclodextrin hydrochloride (I).





β-CD-O-CH_2CH=$CHCH_2O$-NH_2.HCl

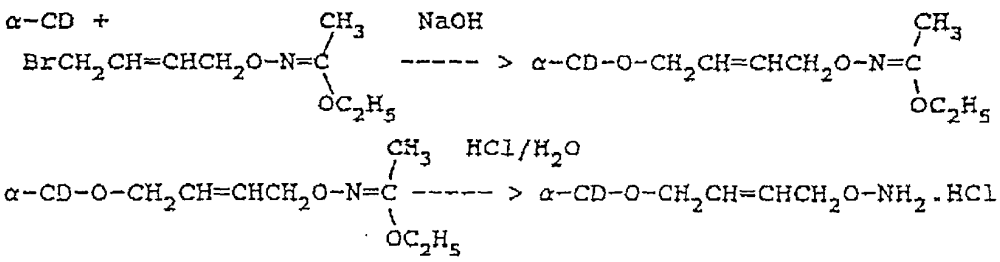
1. 3.1 g (14 mmoles) of 1-ethoxyethylideneaminooxy-4-bromo-butene-2 *(Khomutov A.R. and Khomutov R.M. (1986) Bioorgan.Khim., Russ., v.12, No.12, p.1662-1674)* was added to a solution of 2.26 g (2 mmoles) of β-cyclodextrin in a mixture of 18.7 ml water and 1.3 ml of 10 N NaOH and heated under nitrogen on a boiling water bath with intensive stirring until the pH turned neutral (usually 60-90 min). On cooling an oil separated. The product was washed with cold water and dissolved in 50 ml of i-PrOH and 4 ml of 5.0 N HCl was added. After a 30-minute incubation at 20°C, the liquid was decanted and the residual oil crystallized with absolute i-PrOH. The precipitation was filtered and washed with absolute i-PrOH and dried over P_2O_5/KOH in vacuo, resulting in 2.80 g (90% yield) of (I). The amount of aminooxy groups was determined *(Korpela T.K. and Makela M.J. (1981) Anal.Biochem. v.110, No.2, p.251-258)* and was 2.8 mmols/g, the low value indicating that only primary hydroxyl groups had reacted. NMR (Jeol-400, DMSO-d_6) :

2. 7.7 g (35 mmoles) of 1-ethoxyethylideneaminooxy-4-bromobutene-2 was added to a solution of 5.6 g (5 mmoles) of β-cyclodextrin in a mixture of 70 ml of water and 3.4 ml

of 10 N NaOH and mixed with a magnetic stirrer at 20°C. After two days, 10 ml of i-PrOH was added and stirring continued at 20°C until the pH turned neutral (usually about 5-8 days). The solution was evaporated to dryness in vacuo, the residual oil washed with cold water and dissolved in 50 ml of i-PrOH and 10 ml of 5.0 N HCl was added. After a 30 minute incubation at 20°C, the liquid was decanted and the residual oil crystallized with absolute i-PrOH. The precipitation was filtered and washed with absolute i-PrOH and dried over P_2O_5/KOH in vacuo, resulting in 3.56 g (50% yield) of (I). The amount of aminooxy groups determined as above was 2.26 mmols/g. NMR data identical to that in ex.I.1.

Example II

4-Aminooxy-2-butenyl-α-cyclodextrin hydrochloride (II).

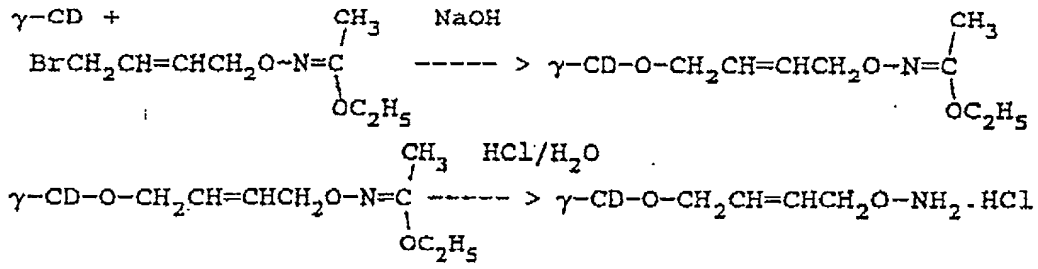


2.8 g (12 mmoles) of 1-ethoxyethylideneaminooxy-4-bromo-butene-2 was added to a solution of 1.96 g (2 mmoles) of α-cyclodextrin (Sigma) in a mixture of 18.9 ml of water and 1.1 ml of 10 N NaOH and heated under nitrogen on a boiling water bath with intensive stirring until pH turned neutral (usually 60-90 min). The oil which separated on cooling was washed with cold water and dissolved in 50 ml i-PrOH. To this solution 4 ml of 5.0 N HCl was added. After 30 min incubation at 37°C, the liquid was decanted and the residual oil crystallized with i-PrOH. The precipitation was filtered, washed with absolute i-PrOH and dried over

P_2O_5/KOH in vacuo resulting in 2.21 g (69% yield) of II. The amount of aminooxy groups determined as above was 3,25 mmoles/g. NMR (Jeol-400, DMSO-d_6) :

Example III

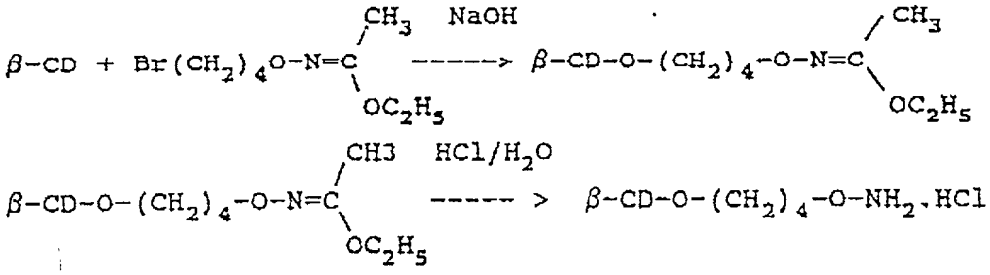
4-Aminooxy-2-butenyl-γ-cyclodextrin hydrochloride (III).



3.54 g (16 mmoles) of 1-ethoxyethylideneaminooxy-4-bromobutene-2 was added to a solution of 2.6 g (2 mmoles) of γ-cyclodextrin (Fluka) in a mixture of 18.5 ml of water and 1.5 ml of 10 N NaOH and heated under nitrogen on a boiling water bath with intensive stirring until the pH turned neutral (usually 60-90 min). The oil which separated on cooling was washed with cold water and dissolved in 50 ml of i-PrOH and 4 ml of 5.0 N HCl was added. After a 30-minute incubation at 20°C, the liquid was decanted and the residual oil crystallized with i-PrOH. The precipitation was filtered and washed with abs. i-PrOH and dried over P_2O_5/KOH in vacuo, resulting in 3.76 g (95% yield) of III. The amount of aminooxy groups determined as above was 2,86 mmoles/g. NMR (Jeol-400, DMSO- d_6):

Example IV

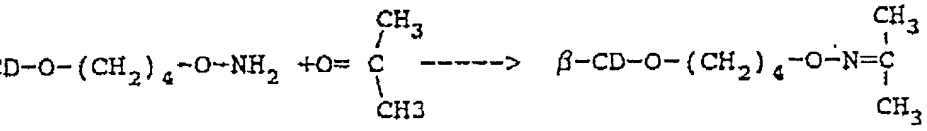
4-Aminooxybutyl-β-cyclodextrin hydrochloride (IV).



3.1 g (14 mmoles) of 1-ethoxyethylideneaminooxybutylbromide *(Nedospasov A.A. and Khomutov R.M. (1976) Izv. AN SSSR Ser. Khim. (in Russian) No.9, p.2113-2115)* was added to a solution of 2.26 g (2 mmoles) of β-cyclodextrin in a mixture of 18.7 ml water, 0.21 g (1.4 mmoles) of NaI and 1.3 ml of 10 N NaOH and heated under nitrogen on a boiling water bath with intensive stirring until the pH turned neutral (12-18 hrs). The oil separated on chilling was washed with cold water and dissolved in 50 ml of i-PrOH. To this solution 4 ml of 5,0 N HCl was added, after 30 min incubation at 20°C the liquid was decanted and the residual oil crystallized upon abs. i-PrOH treatment. The precipitation was filtered and washed with abs. i- PrOH and dried over P_2O_5/KOH in vacuum, that gave 1.66 g (58% yield) of IV. The amount of aminooxy groups determined as above was 2.20 mmoles/g. NMR (Jeol-400, DMSO-d_6) : 10.99 (m, H_2N-O-), 4.84 (m, C_1-H), 4.02 (m, H_2NO-CH_2-), 3.76-3.38 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 1.62 (m, -CH_2-CH_2-). NMR (Jeol-400, D_2O) : 4.92 (m, C_1-H), 3.95 (m, H_2NO-CH_2-), 3.71-3.45 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 1.59 (m, -CH_2-CH_2-).

Example V

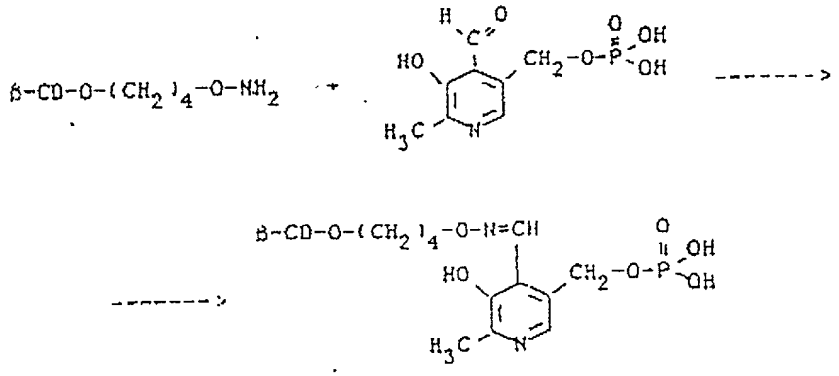
Acetonoxime of 4-Aminooxybutyl-β-cyclodextrin (V).



To a solution of 1.5 g of (IV) in 15 ml of H_2O-aceton mixture (1:1, V/V), diluted aqueous ammonia was added to a pH of 5-6. Then the reaction mixture was incubated for 2 h at 20°C. After evaporation to dryness, the residue was treated with water, the semi-solid product was separated and crystallized twice from water. The precipitate was filtered off, dried in vacuo over P_2O_5/KOH and 1.1 g (7 % yield) of (V) was obtained. NMR (Jeol-400, DMSO-d_6) : 4.83 (m, C_1-H), 3.92 (m, =NO-CH_2-), 3.75-3.22 (m, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 1.77 (m, $(CH_3)_2C$=), 1.59 (m, -CH_2-CH_2-).

Example VI

Pyridoxal-5'-phosphate oxime of 4-aminooxybutyl-β-cyclo-dextrin (VI).

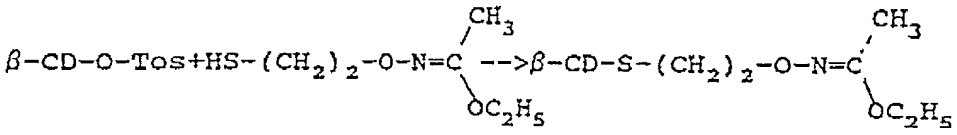


To a solution of 10.6 mg pyridoxal-5'-phosphate ("Merck") in 1.24 ml 0.1 N NaOD in D_2O, 20 mg of (IV) was added and

the reaction mixture was incubated for 2 hr. at 20°C. The compound (VI) was obtained with a yield being close to quantative. NMR (Jeol-400, D_2O) : 8.39 (m, H-C=N-O-), 7.70 (m, α-H), 4.85 (m, C_1-H), 4.74 (m, $-CH_2$-O-P-), 4.33 (m, H_2NO-CH_2-), 3.72-3.32 (m, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 2.58 (m, α-CH_3), 1.58 (m, $-CH_2-CH_2$-).

Example VII

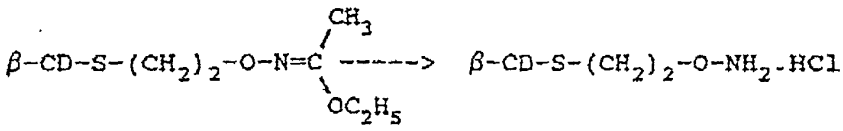
Mono-6-(2-ethoxyethylideneaminooxyethyl)thio-6-deoxy-β-cyclodextrin (VII).



To a solution of 0.74 g (4.5 mmoles) of 2-ethoxyethylideneamino-oxyethylmercaptane *(Khomutov A.R. and Khomutov R.M. (1986) Bioorg. Khim. (Russ.) v.12, No.12, p.1662-1674)* in 2.0 ml abs. MeOH was added 2.22 ml of 2 M MeONa/MeOH, after evaporation in vacuum to dryness the residue was dissolved in a mixture of 9.5 ml abs. DMSO and 0.5 ml MeOH and added to a solution of 1.95 g (1.5 mmoles) of mono-6-O-tosyl-β-cyclodextrin *(Matsui Y. and Okimoto A. (1978) Bull.Chem.Soc. (Japan) v.51, No.10, p.3030-3034)* in 15 ml abs. DMSO. The reaction was kept for 8 hr at 20°C, then 1.2 ml of 2 M AcOH in DMSO was added and the solution evaporated to dryness in vacuum. The residual oil solidified after water treatment, the precipitate was filtered off, washed with cold water, recrystallized twice from water and dried in vacuum over P_2O_5/KOH to give 1.3 g (yield 67 %) of VII. NMR (Jeol-400, DMSO-d_6) : 4.86 (m, C_1-H), 3.97 (q, CH_3-CH_2-O-), 3.94 (t, =NO-CH_2-), 3.79-3.33 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 2.79 (m, $-CH_2-CH_2$-S-), 1.87 (s, CH_3-), 1.23 (t, CH_3-CH_2-O-).

Example VIII

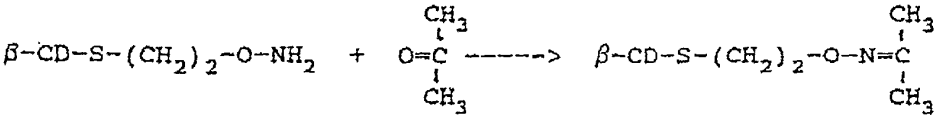
Mono-6-(2-aminooxyethyl)thio-6-deoxy-β-cyclodextrin hydrochloride (VIII)



1.25 g (1.0 mmoles) of (VII) were suspended in 20 ml of 1 N HCl, heating to 50°C gave clear solution, which was evaporated to dryness in vacuum. The residual oil solidified upon treatment with abs. i-PrOH. The precipitate was filtered off, washed with abs. i-PrOH and dried over P_2O_5/KOH in vacuum that gave 0.80 g (65% yield) of (VIII). The amount of aminooxy groups determined as above was 0.88 mmoles/g. NMR (Jeol-400, DMSO-d_6) :4.85 (m, C_1-H), 4.12 (t, H_2NO-CH_2-), 3.82-3.33 (mm, C_3-H, C_6-HC_5-H-C_2-H,C_4-H), 2.86 (m, CH_2-CH_2-S)

Example IX

Acetonoxime of mono-6-(2-aminooxyethyl)thio-6-deoxy-β-cyclodextrin (IX).

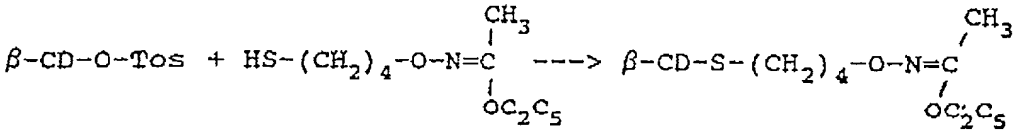


To a solution of 0.62 g (0.5 mmoles) of (VIII) in 8.0 ml of a H_2O-acetone cocktail (1:1, V/V), a diluted water NH_3 solution was added to pH 5-6 and the reaction mixture was incubated for 2 h at 20°C. After evaporation to dryness,

the residue was crystallized twice from water. The precipitate was filtered off, dried in vacuum over P_2O_5/KOH and 0.5 g (80 % yield) of IX as obtained. NMR (Jeol-400, DMSO-d_6) : 4.85 (m, C_1-H), 4.04 (t, =NO-CH_2-), 3.79-3.36 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 2.77 (m, CH_2-CH_2-S), 1.80 (d, CH_3-).

Example X

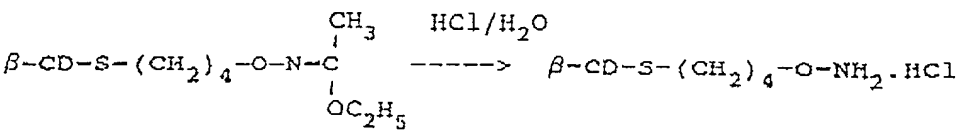
Mono-6-(4-ethoxyethylideneaminooxybutyl)thio-6-deoxy-β-cyclodextrin (X)



Mono-6-(4-ethoxyethylideneaminooxybutyl)thio-6-deoxy-β-cyclodextrin was obtained as is described for (VII) starting from 1.95 g (1.5 mmoles) of mono-6-O-tosyl--β-cyclodextrin and 0.85 g (4.5 mmoles) of 4-ethoxyethylideneaminooxyethylmercaptan *(Nedospasov A.A. and Khomutov R.M. (1976) Izv. AN SSSR Ser. Khim. (in Russian) No.9, p.2113-2115)* that gave 1.56 g (80 % yield) of (X). NMR (Jeol-400, DMSO-d_6) : 4.84 (m, C_1-H), 3.95 (q, CH_3-CH_2-O--), 3.80 (t, =NO-CH_2-), 3.75-3.31 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 2.68 (m, CH_2-CH_2-S) 1.87 (d, CH_3-), 1.56 (m, -CH_2-CH_2), 1.23 (t, CH_3-CH_2-O-).

Example XI

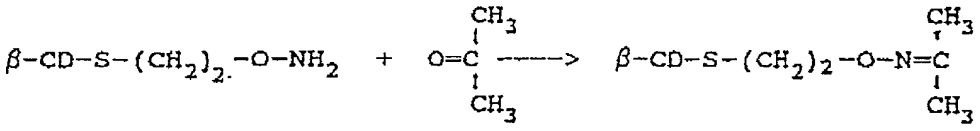
Mono-6-(4-aminooxybutyl)thio-6-deoxy-β-cyclodextrin hydrochloride (XI)



Mono-6-(4-aminooxybutyl)thio-6-deoxy-β-cyclodextrin hydrochloride was obtained as is described for (VIII), starting from 1.3 g (1.0 mmoles) of (X) that gave 1.0 g (75 % yield) of (XI). NMR (Jeol-400, DMSO-d_6) : 10.85 (m, H_2NO-), 4.83 (m, C_1-H), 3.99 (m, H_2NO-CH_2-), 3.63-3.31 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 1.59 (m, $-CH_2-CH_2-$).

Example XII

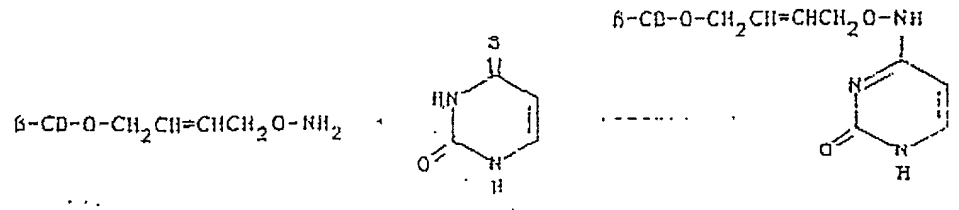
Acetonoxime of mono-6-(2-aminooxyethyl)thio-6-deoxy-β-cyclodextrin (XII).



The acetonoxime of mono-6-(2-aminooxyethyl)thio-6-deoxy-β-cyclo-dextrin was obtained as is described for (IX) starting from 0.7 g of (XI) that gave 0.55 g (78 % yield) of (XII). NMR (Jeol-400, DMSO-d_6) :4.82 (m, C_1-H), 3.89 (t, $=NO-CH_2$-), 3.61-3.32 (mm, C_3-H, C_6-H, C_5-H, C_2-H, C_4-H), 2.92 (m, CH_2-CH_2-S), 1.78 (d, CH_3-), 1.52 (m, $-CH_2-CH_2-$).

Example XIII

Reaction of I with 4-thiouracil

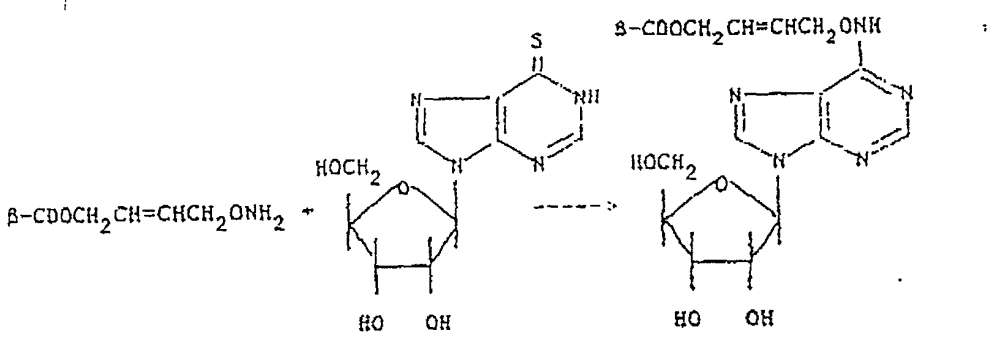


A 1 mM solution of 4-thiouracil (Lachema, Brno, Czechoslovakia) was incubated at 20°C within a 0.1 M solution of 4-aminooxy-2-butenyl-β-CD (I) at neutral pH. The UV-spectra were recorded at certain time intervals using

cuvettes of 1 mm optical path length (Figure 1a). This reaction was compared with the reaction of 4-thiouracil with 1-aminooxybutane under the same reaction conditions (Fig.1b). The results show significantly higher velocity of reaction with the aminooxy-2-butenyl-β-CD.

Example XIV

Reaction of I with 6-mercaptopurine riboside



A 1 mM solution of 6-mercaptopurine riboside (Sigma Chem.Co., USA) was incubated at 20°C within 0.1 M of 4-aminooxy-2-butenyl-β-CD (I). At certain time intervals UV-spectra were recorded in cuvettes of 1 mm optical path (Fig. 2a). The similar reaction with 1-aminooxybutane (Fig. 2b) showed drastically higher reaction rates with the CD-derivative.

WHAT IS CLAIMED IS:

1. Aminooxy-cyclodextrin derivatives of the formula 1:

$$CD - (X - Y - ONH_2)_n \quad , \qquad (1)$$

wherein
CD is a mono- or polydeoxy α-, β- or γ-cyclodextrin, carrying in its 6-, 3- and/or 2-position the aminooxy function containing group ($X-Y-ONH_2$), and optionally carrying further substituents different from ($X-Y-ONH_2$) in their 6-, 3- and/or 2-positions, and wherein Y is a linker group between the aminooxy group and the mono- or polydeoxy-CD-group,
X is a functional group or an atom necessary to connect the linker Y and the deoxy CD group, or Y is a direct bond when X is a direct bond,
and n is ≥ 1, but ≤ 24, 21 and 18 for α-, β- or γ-cyclodextrin, respectively, as well as the aminooxy protected derivatives thereof, especially ethoxy-ethylidene protected aminooxy and acetone oxime derivatives thereof.

2. A derivative according to claim 1, wherein Y and X are both direct bonds.

3. A derivative according to claim 1 or 2, wherein one or more of the primary hydroxy groups at a 6-position of α-, β- or γ-CD are substituted with a $X-Y-ONH_2$ fragment, wherein X and Y have the meaning of claim 1.

4. A derivative according to any one of claims 1 and 3, wherein Y is a linear or branched alkylene, alkenylene with one or more double bounds which may be either isolated or conjugated, alkynylene with one or more triple bonds which may be either isolated or conjugated, or arylene or arylalkylene fragments where aryl may be substituted or not substituted, whereby the alkylene, alkenylene and alkynyle-

ne fragments may be linear or branched and preferably contain 2-12 C-atoms in the chain, and one or more of the chain members (methylene groups) may be replaced by -NH-, -O-, -S-, -S-S-, -C(O)NH, -C(O)O-, -OP(O)(OH)O-, -S(O)-, SO_2-, -CHR-, where R is preferably alkyl, aryl, -OR', $-NH_2$, -NHR', $-NR'_2$, -OH, -COOH, or $-ONH_2$ groups and where R' is alkyl, aryl, or acyl.

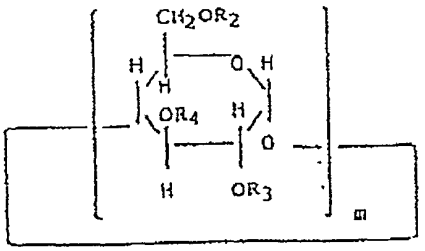
5. A derivative according to any one of the claims 1, 3 and 4, wherein X is -O-, -S-, -NH-, -NR"-, -OCO-, -NH-O-, =NO-, -NHC(O)-, -OP(O)(OH), -R"C=NO-, where R" is linear or branched lower alkyl.

6. A derivative according to the claims 4 or 5, wherein Y is alkylene containing 2-12 C-atoms, wherein one or more of the chain members may be replaced by -NH-, -O-, -S-, -C(O)NH-, -C(O)O-, or CHR_1 wherein R_1 is methyl, ethyl or propyl and X is -O-, -S-, -NH-, -OC(O)-, and -NH-C(O)-.

7. Any compound according to claim 1-6, wherein one or more of the hydroxyl groups at 6-, 3-, and/or 2- position(s) are substituted with a group, for example, H_2N- , HS-, -COOH, alkoxy- , such as C_1 - C_6- alkoxy- , aryloxy-, wherein aryl is preferably phenyl, benzyl, or tolyl, or with acyloxy group, wherein acyl preferably originates from C_1 - C_6- carboxyl, or benzoic acids, and wherein alkyl-, aryl-, and acyloxy- can additionally contain functional groups like H_2N- , HS-, -COOH in their structure, in side chain or in aromatic ring.

8. Method according to claim 1 or 3 for preparing compound of formula 1, wherein X is O, and wherein:

a) cyclodextrin of formula (3)



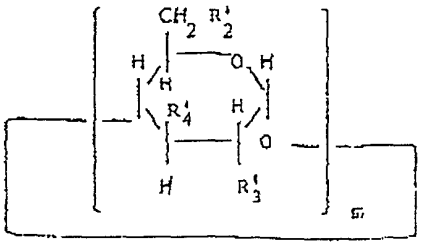
(3)

including R_2, R_3, and R_4 are hydroxyl groups or substituents defined in claim 7, exemplified by unsubstituted alkoxy, like C_1 - C_6- alkoxy or aryloxy like phenyl-, benzyl-, tolyl-, or acyloxy, in which substituents' functional groups, if they exist, are protected whenever necessary, whereby at least one of the positions 6, 3, and/or 2 contain hydroxyl group, preferably 6- hydroxy group, is alkylated with a compound according to formula (3'):

$$Z - Y - ON = C(CH_3) W \qquad (3')$$

wherein W means group $-OC_2H_5$ or $-CH_3$, m and Y are as defined in claims 1 or 3, and Z is a reactive group, preferably Cl, Br, I, tosyl, mesyl or epoxy group, and optionally protecting group(s) is/are removed, or

b) a cyclodextrin derivative of formula (4) is alkylated



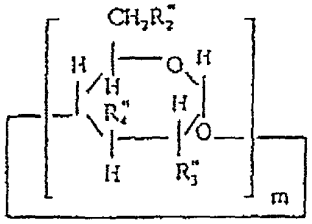
(4)

wherein R'_2, R'_3, R'_4 are hydroxy or activated groups like tosyl, mesyl, halogen, ester, epoxy, preferably tosyl or halogen, possibly bound through a linker group, like alkylen, or substituent as defined in claim 7, said substituent being in a protected form if necessary, whereby the CD-derivative contains at least one of said activated groups with the compound of formula (4')

$$HX - Y- ON = C (CH_3) W \qquad (4')$$

wherein X and Y are as in claim 1, or as in 3 and 4, and X is preferably S or HN- fragment and Y has the meaning defined in claim 6, and W is defined as above, and protecting group(s) is/are possibly removed if necessary, or

c) a cyclodextrin derivative of compound with formula (5)



(5)

wherein at least one of the groups R''_2, R''_3, and R''_4 mean thiol-, amino-, karboxy- etc. group possibly linked directly to deoxy-CD-ring, or mean alkylenoxy- or acyloxy groups which contain at least one thiol-, amino-, karboxy-, etc. group, or their derivative, and the remaining funtional groups are hydroxyl groups or they have the meaning described in claim 7 for the substituents, and exist, if necessary, in a protected form, typical example being unsubstituted alkoxy, aryloxy, or acyloxy, modified with an appropriate aminooxy protected substituted hydroxylamine according to formula (3'), after which the protecting

group(s) are removed, or

d) CD-derivative of formula (5), which contains one or more of keto or aldehyde groups, possibly bound through a linker group, is allowed to react with bisaminooxy alkanes of formula (5')

$H_2NO\ (CH_2)_tONH_2$ (5')

wherein t is 2-12, and wherein one of the methylene groups can be substituted with oxygen or sulfur atom, or wherein -NH- or -S-S- groups, and a protecting group is removed if necessary.

9. The use of any of the CD-derivatives of claims 1-7 for preparation of oximes with ketones or aldehydes, for preparation of aminooxy derivatives of nucleotide- and nucleoside pyrimidines or purines, or for preparation of inclusion complexes with guest molecules by said CD-derivatives.

10. Oximes of any one of the aminooxy-CDs of claim 1-7 with a synthetic or natural aldehydes or ketones.

11. Derivatives of nucleotide or nucleoside pyrimidines or purines with aminooxy-CDs, wherein aminooxy group is linked to heterocyclic ring, preferably through pyrimidine C-4 and purine C-6, and wherein pyrimidine and purine are preferably cytosine or adenine as such or as their derivatives.

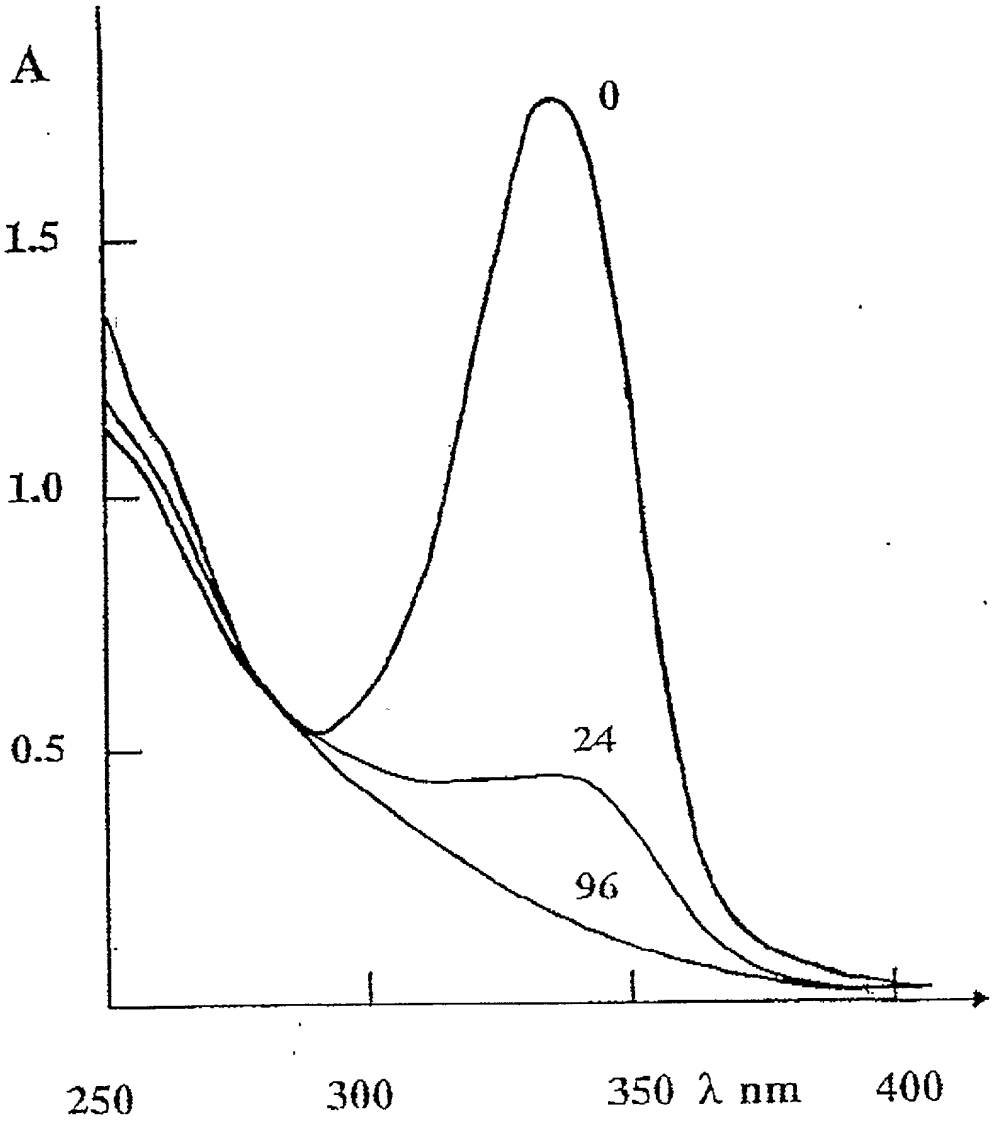


Figure 1 a

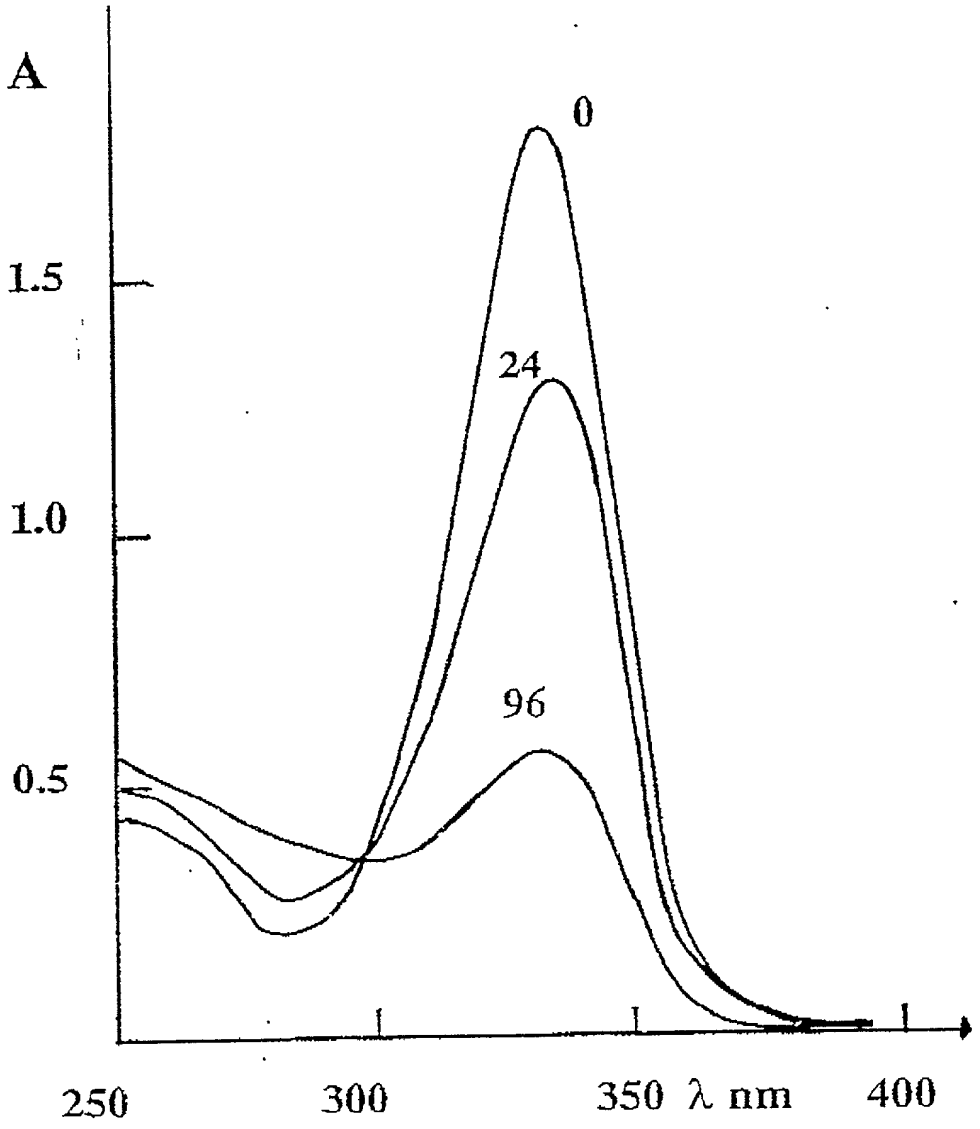


Figure 1 b

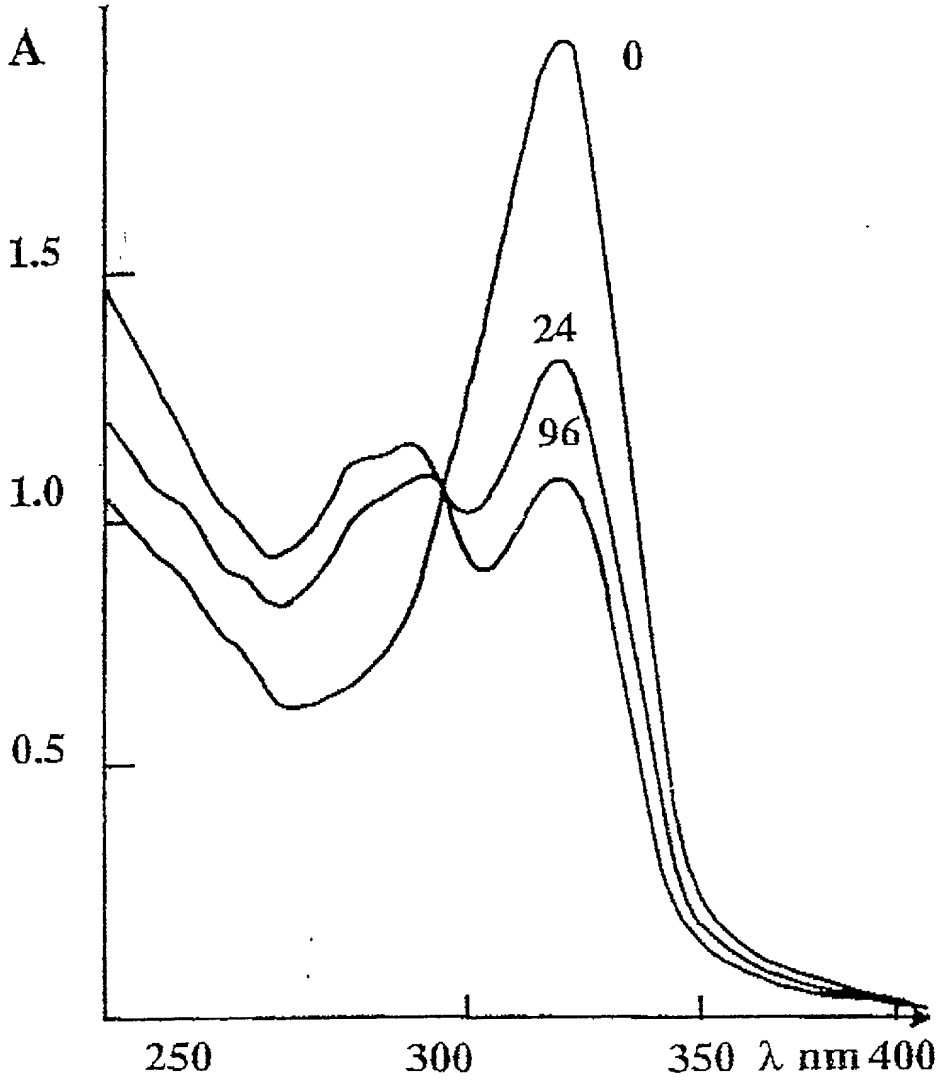


Figure 2 a

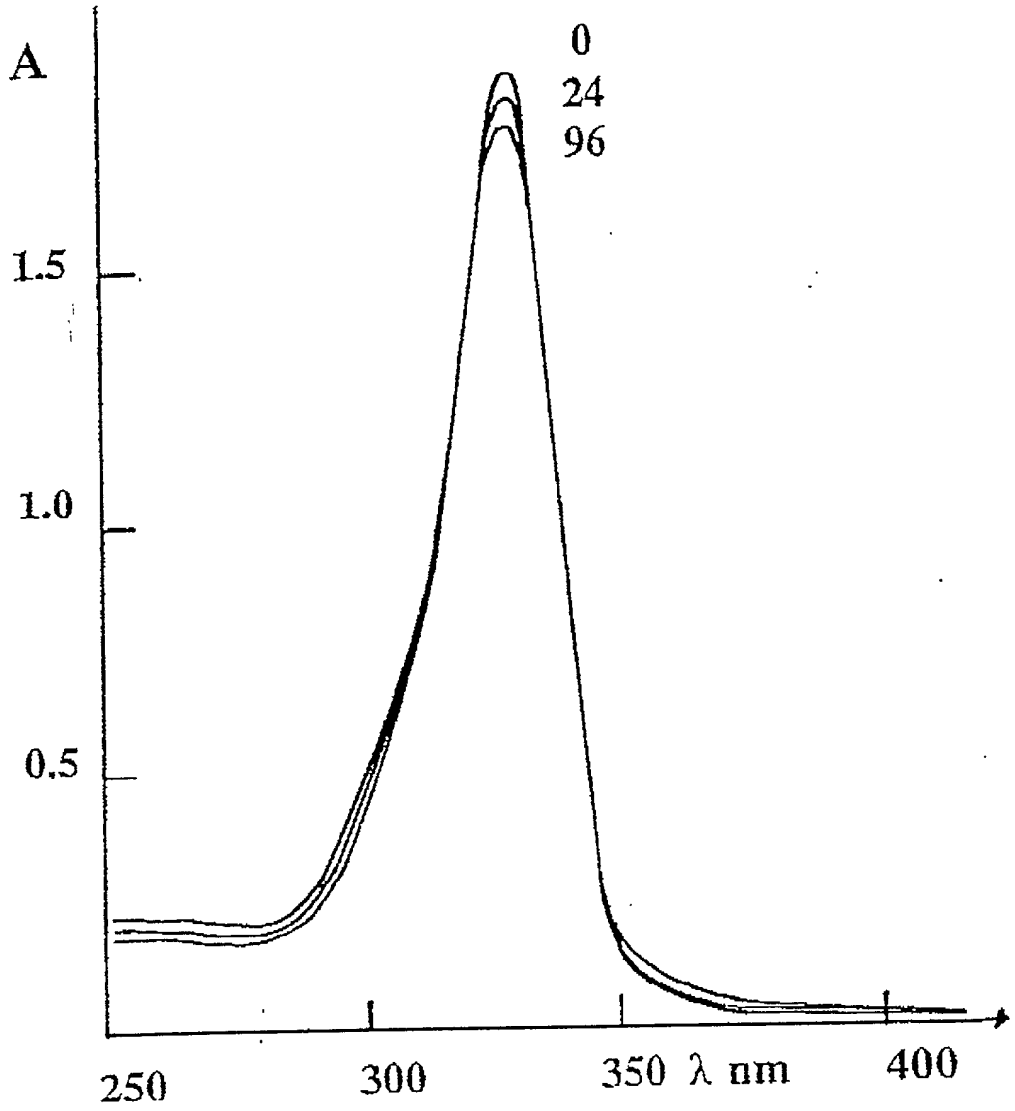


Figure 2 b

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: → NOVEL DERIVATIVES OF CYCLODEXTRINS

the specification of which is attached hereto. If not attached hereto,

Fill in Appropriate Information — For Use Without Specification Attached: →

the specification was filed on _____ as United States Application Number _____ ; and amended on _____ (if applicable); and/or the specification was filed on March 4, 1999 as PCT International Application Number PCT/FI99/00167; and was amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate) →

Prior Foreign Application(s) (Number)	(Country)	(Month / Day / Year Filed)	Priority Claimed	
980489	Finland	3/4/1998	☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

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_____ (Application Number) _____ (Filing Date)

_____ (Application Number) _____ (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

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Country	Application Number	Date of Filing (Month / Day / Year)

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Insert Prior U.S. Application(s): (if any) →

(Application Number)	(Filing Date)	(Status — patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

16 –

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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1-00

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* DATE OF SIGNATURE